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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,214	06/14/2001	Michael Probst-Kepper	L0461/7102	6577

23628 7590 03/01/2006

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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7590 12/07/2005

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
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DATE MAILED: 12/07/2005

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09/786,214	06/14/2001	Michael Probst-Kepper	L0461/7102	6577

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	09/786,214	PROBST-KEPPER ET AL.
	Examiner: DiBrino Marianne	Art Unit: 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,58,59 and 65-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,58,59 and 66-70* is/are rejected.

7)☐ Claim(s) *3,65 and 71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 12/1/04 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election of Group I (claims 1-3, 7, 8, 58 and 59), and species of polypeptide comprising SEQ ID NO: 5 in Applicant's response filed 2/6/04.

Claims 1-3, 7, 58, 59 and 65-71 are currently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: The first line of the specification claims priority to Application serial no. 60/099,077 filed September 4, 1998 that is not listed in the declaration.

The Examiner acknowledges Applicant's statement in the amendment filed 12/1/04 that an application data sheet was filed, however, the said application data sheet does not appear to have been filed.

The following are new grounds of rejection necessitated by Applicant's amendment filed 12/1/04.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 7, 58, 59 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed: (1) isolated polypeptide/composition thereof comprising the amino acid sequence of a "functional amino acid substitution variant" of SEQ ID NO: 12 "that retains immunogenicity", (2) or a fragment having, i.e., comprising, at least 14 consecutive amino acid residues of SEQ ID NO: 5, (3) a composition comprising an

immunogenic fragment of SEQ ID NO: 5, or which said composition comprises an immunogenic fragment, said immunogenic fragment comprises the amino acid sequence of SEQ ID NO: 12, (4) an isolated immunogenic polypeptide comprising the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 9 or SEQ ID NO: 12.

The instant claims encompass: (1) an isolated polypeptide/composition thereof comprising the amino acid sequence of a "functional amino acid substitution variant" of SEQ ID NO: 12 "that retains immunogenicity", i.e., it can stimulate an antibody response or it can stimulate a T cell response to a different HLA/T cell combination than SEQ ID NO: 12, (2) a fragment having, i.e., comprising, at least 14 consecutive amino acid residues of SEQ ID NO: 5 that does not contain SEQ ID NO: 12 and does not stimulate the same HLA/CTL combination, (3) a composition comprising an immunogenic fragment of SEQ ID NO: 5 that does not contain SEQ ID NO: 12 and does not stimulate the same HLA/CTL combination, or which said composition comprises an immunogenic fragment, said immunogenic fragment comprises the amino acid sequence of SEQ ID NO: 12 but does not further comprise flanking amino acid residues present in SEQ ID NO: 5, (4) an isolated immunogenic polypeptide comprising the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 9 or SEQ ID NO: 12 that does not further comprise flanking amino acid residues present in the alt.M-CSF sequence, i.e., that is not a subsequence of alt.M-CSF tumor rejection protein. In addition, the said peptide/fragment composition, thereof can comprise amino acid residues that flank the said sequences in the peptide or protein of origin, or can be any number of undisclosed and unrelated sequences or can be non-peptidic in nature. There is insufficient disclosure in the specification on the said peptide/fragment/composition including vaccine thereof.

The specification discloses that expression of alt.M-CSF is detected in normal hepatocytes and not exclusively in [renal] tumor cells (page 42 at lines 16-20). The specification further discloses that the peptide SEQ ID NO: 12 is derived from the translation of an alternative open reading frame of the normal human M-CSF cDNA and is recognized by a CTL line from a renal carcinoma patient as well as on two allogeneic HLA-B*3501 positive renal cell carcinoma lines (page 40 at lines 13-16). The specification further discloses that N- or C-terminal truncations of SEQ ID NO: 12 failed to sensitize allogenic HLA-B*3501 positive EBV-B cells, SEQ ID NO: 12 appearing to be the minimal peptide (page 40 at lines 4-12).

The specification discloses that functional a variant of an alt.M-CSF immunogenic polypeptide is a molecule which contains one or more modifications to the primary amino acid sequence of an alt.M-CSF immunogenic polypeptide and retains the HLA class I binding properties disclosed as well as the ability to stimulate proliferation and/or activation of $CD8^+$ T lymphocytes (page 11 at lines 10-14). The specification discloses that modifications to create a functional variant include enhancing a property such as peptide stability in an expression system, more stable peptide/HLA binding, or providing a novel activity or property such as the addition of an antigenic epitope or a detectable moiety, or providing a different amino acid sequence that produces the same or similar T cell stimulatory properties (page 11 at lines 14-20). The specification discloses that the amino acid sequences of alt.M-CSF immunogenic

polypeptides may be of natural or non-natural origin, that is they may comprise a natural alt.M-CSF immunogenic polypeptide molecule or they may comprise a modified sequence as long as the amino acid sequence retains the ability to stimulate CTL when presented and binds to an HLA Class I molecule such as HLA-B*3501 (page 11 at lines 28-32).

The specification discloses that methods for identifying functional variants of an alt.M-CSF immunogenic polypeptide include selecting an alt.M-CSF polypeptide, an HLA molecule that binds the said polypeptide, and a T cell that is stimulated by the said polypeptide or a fragment thereof, adding, deleting or substituting a first or second amino acid residue and testing for binding to HLA and/or stimulation of a T cell (paragraph spanning pages 6 and 7).

The specification discloses other methods for identifying functional variants of the alt.M-CSF immunogenic polypeptides rely upon the development of amino acid sequence motifs to which potential epitopes may be compared or that motif analysis may be used in design of such polypeptides, experimental ranking schemes may be used and the stimulation of the T cell are determined according to standard procedures (page 13 at lines 13-32, page 14 at lines 1-22 and page 15 at lines 3-12).

The specification discloses methods for identifying a candidate mimetic of an alt.M-CSF polypeptide that is not necessarily a peptide, but is a functional variant (page 8 at lines 1-12). The specification discloses that exemplary polypeptides are processed translation products of SEQ ID NO: 4 and that the said polypeptides may be any length as long as they are processed to a final form that encompasses SEQ ID NO: 12. The specification discloses that SEQ ID NO: 12 may have added amino acid residues that correspond to the alt.M-CSF polypeptide of SEQ ID NO: 5, or may be unrelated (page 10 at lines 11-24).

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "functional amino acid substitution variant that retains immunogenicity" or "a fragment thereof having at least 14 consecutive amino acid residues of SEQ ID NO: 5" or "composition comprising an immunogenic fragment of SEQ ID NO: 5" does not describe the claimed peptide/fragment/composition thereof, except by the property of retaining some form of immunogenicity, or containing at least 14 consecutive amino acid residues of SEQ ID NO: 5 which may not include SEQ ID NO: 12, or that comprises any immunogenic fragment of SEQ ID NO: 5 that may not include SEQ ID NO: 12 that stimulates a humoral or cellular immune response. It does not specifically define any of the peptides/functional amino acid substitution variants/immunogenic fragments that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, other than the variant has to bind some HLA molecule and stimulate some T cell or some antibody response. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a definition by

function does not suffice to define the genus because it is only an indication of what the property the peptide has, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 12/1/04 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on pages 5-7.

It is the Examiner's position that claim 1 recites an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 5, or a fragment thereof having at least 14 consecutive amino acids of SEQ ID NO: 5, i.e., the polypeptide comprises the fragment, and so the sequence of the said isolated polypeptide can be of any length or composition flanking either end of the said fragment. It is the Examiner's further position with regard to Applicant's argument to an isolated immunogenic polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 12, that the amino acid residues flanking the polypeptide can be any amino acid residues up to any length.

6. Claims 1, 2, 7, 58, 59 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and/or using a peptide consisting of the sequence of SEQ ID NO: 5, 9 or 12, does not reasonably provide enablement for making and/or using an isolated polypeptide/composition thereof comprising the amino acid sequence of (1) a "functional amino acid substitution variant" of SEQ ID NO: 12 "that retains immunogenicity", i.e., it can stimulate an antibody response or it can stimulate a T cell response to a different HLA/CTL cell combination than SEQ ID NO: 12, (2) a fragment having, i.e., comprising, at least 14 consecutive amino acid residues of SEQ ID NO: 5 that does not contain SEQ ID NO: 12 and does not stimulate the same HLA/CTL combination, (3) a composition comprising an immunogenic fragment of SEQ ID NO: 5 that does not contain SEQ ID NO: 12 and does not stimulate the same HLA/CTL combination, or which said composition comprises an immunogenic fragment, said immunogenic fragment comprises the amino acid sequence of SEQ ID NO: 12 but does not further comprise flanking amino acid residues present in SEQ ID NO: 5, (4) an isolated immunogenic polypeptide comprising the

amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 9 or SEQ ID NO: 12 that does not further comprise flanking amino acid residues present in the alt.M-CSF sequence, i.e., that is not a subsequence of alt.M-CSF tumor rejection protein. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed invention can be made and or used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses that expression of alt.M-CSF is detected in normal hepatocytes and not exclusively in [renal] tumor cells (page 42 at lines 16-20). The specification further discloses that the peptide SEQ ID NO: 12 is derived from the translation of an alternative open reading frame of the normal human M-CSF cDNA and is recognized by a CTL line from a renal carcinoma patient as well as on two allogeneic HLA-B*3501 positive renal cell carcinoma lines (page 40 at lines 13-16). The specification further discloses that N- or C-terminal truncations of SEQ ID NO: 12 failed to sensitize allogenic HLA-B*3501 positive EBV-B cells, SEQ ID NO: 12 appearing to be the minimal peptide (page 40 at lines 4-12).

The specification discloses that functional a variant of an alt.M-CSF immunogenic polypeptide is a molecule which contains one or more modifications to the primary amino acid sequence of an alt.M-CSF immunogenic polypeptide and retains the HLA class I binding properties disclosed as well as the ability to stimulate proliferation and/or activation of $CD8^+$ T lymphocytes (page 11 at lines 10-14). The specification discloses that modifications to create a functional variant include enhancing a property such as peptide stability in an expression system, more stable peptide/HLA binding, or providing a novel activity or property such as the addition of an antigenic epitope or a detectable moiety, or providing a different amino acid sequence that produces the same or similar T cell stimulatory properties (page 11 at lines 14-20). The specification discloses that the amino acid sequences of alt.M-CSF immunogenic polypeptides may be of natural or non-natural origin, that is they may comprise a natural alt.M-CSF immunogenic polypeptide molecule or they may comprise a modified sequence as long as the amino acid sequence retains the ability to stimulate CTL when presented and binds to an HLA Class I molecule such as HLA-B*3501 (page 11 at lines 28-32).

The specification discloses that methods for identifying functional variants of an alt.M-CSF immunogenic polypeptide include selecting an alt.M-CSF polypeptide, an HLA molecule that binds the said polypeptide, and a T cell that is stimulated by the said polypeptide or a fragment thereof, adding, deleting or substituting a first or second amino acid residue and testing for binding to HLA and/or stimulation of a T cell (paragraph spanning pages 6 and 7).

The specification discloses other methods for identifying functional variants of the alt.M-CSF immunogenic polypeptides rely upon the development of amino acid sequence motifs to which potential epitopes may be compared or that motif analysis may be used in design of such polypeptides, experimental ranking schemes may be used and the stimulation of the T cell are

determined according to standard procedures (page 13 at lines 13-32, page 14 at lines 1-22 and page 15 at lines 3-12).

The specification discloses methods for identifying a candidate mimetic of an alt.M-CSF polypeptide that is not necessarily a peptide, but is a functional variant (page 8 at lines 1-12). The specification discloses that exemplary polypeptides are processed translation products of SEQ ID NO: 4 and that the said polypeptides may be any length as long as they are processed to a final form that encompasses SEQ ID NO: 12. The specification discloses that SEQ ID NO: 12 may have added amino acid residues that correspond to the alt.M-CSF polypeptide of SEQ ID NO: 5, or may be unrelated (page 10 at lines 11-24).

The specification discloses that alt.M-CSF immunogenic polypeptides such as SEQ ID NO: 12 which are presented by MHC and recognized by CTL can be combined with peptides from other tumor rejection antigens to form polytopes, in order to make composite polypeptides that correspond to the different combination of epitopes representing a subset of tumor rejection antigens expressed in a particular patient or expressed by a tumor type, and the said polytopes administered to induce or enhance an immune response. However, the specification does not disclose use of compositions comprising peptides comprising SEQ ID NO:12 and other tumor associated rejection antigen peptides for testing in vitro or administration in vivo for any patient or tumor type.

The specification discloses that the alt.M-CSF polypeptides may be used for treating a disorder characterized by expression of an alt.M-CSF immunogenic polypeptide, for adoptive transfer, for diagnosis, for production of anti-peptide/HLA mAbs for use in imaging or purification.

Regarding design of peptides, i.e., functional variants, from motif analysis and experimental ranking algorithms the following applies. The claimed invention encompasses fragments of SEQ ID NO: 5 SEQ ID NO: 12, wherein the HLA molecule and peptide binding motif are not specified residues nor are amino acid residues not involved in MHC, i.e., the TCR contact residues. Evidentiary reference Celis et al (Molecular Immunol. 3: 1423-1430, 1994, previously provided) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding peptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA and inducing a CTL response. Celis et al teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens." Evidentiary reference Ochoa-Garay et al (Molecular Immunol. 34(3): 273-281, 1997, previously provided) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL

precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses (especially page 279, last sentence and continuing onto page 280). Evidentiary reference Karin et al (J. Exp. Med. 180: 2227-2237, 1994, previously provided) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. Karin et al teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin et al establish that amino acid residues not recited in the claimed peptide (e.e., amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides recited in the claims are immunogenic.

Evidentiary reference Kast et al (Eur. J. Immunology 1993 23 1189-1192, previously provided) teach that the amino acid residues can exert important effects upon the binding capacity of a peptide, and hence by extension, to potential immunogenicity. Evidentiary reference DiBrino et al (J. Immunology 151(11) 5930-5935, 1993, previously provided) teach that the presence of anchor residues is not sufficient for binding to HLA because peptides with optimal amino acid residues at anchor positions failed to bind. Evidentiary reference Van der Most et al (J. Immunol. 1996, 157: 5543-5554 and Virology 1998, 240: 158-167, previously provided) teach that although an antigenic protein may contain multiple motif-fitting peptides, CTL responses are usually directed against a very limited number of immunodominant epitopes and that immunodominance appears to be determined by a variety of factors including binding affinity to HLA (and motif binding peptides bind with a wide range of affinities due to secondary anchor residues and secondary effects), intracellular processing of peptides determines whether at which level a particular peptide will be presented at the cell surface, and holes in the T cell repertoire restrict CTL responses. Van der Most et al also teach that a peptide from NP with the second highest binding affinity (IC50= 4.8nM) after the immunodominant peptide for L^d, is not recognized by LCMV-restricted CTLs. Evidentiary reference Chang et al (J. Immunol. 1999, 162: 1156-1164, previously provided) teach a peptide that was immunogenic in only a single patient despite similar HLA-binding affinity. Evidentiary reference Vitiello et al (J. Immunol. 1996, 157: 5555-5562, previously provided) teach the importance of not only binding affinity, but also of availability of specific TCRs and antigen processing in the shaping of the final repertoire of CTL specificities. Evidentiary reference Bergman et al (J Virol. 1994, 68(8): 5306-5310, previously provided) teach a discrepancy between antigenicity and immunogenicity, i.e., failure to induce CTL despite highly efficient recognition in vitro.

In addition, evidentiary reference Chaux et al (Int. J. Cancer 77 538-542, 1998, previously provided) teach that it is unclear if peptides from tumor specific proteins possessing anchor residues for binding to class I MHC produce CTL responses in patients vaccinated with the said peptides. Chaux et al further teach that detection of such CTL may require very sensitive detection assays, rather than the conventional assays disclosed in the instant specification. In

addition, Chaux et al teach that it is unclear whether the results seen in vitro are predictive of what occurs in vivo in humans.

Evidentiary reference Shastri et al (J. Immunology 1995, 155: 4339-4346, previously provided) teach that presentation of endogenous peptide/MHC class I complexes is profoundly influenced by specific C-terminal flanking residues in the peptide. The art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr et al, Shastri et al, Bergmann et al, Wang et al, Perkins et al, Theoboald et al and Gileadi et al) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins et al), or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang et al). An undue amount of experimentation would be involved in determining longer peptides from the many possibilities that would be capable of binding to HLA and being recognized by CTL. Evidentiary reference Anderton (Immunology 2001 104 367-376, previously provided) teaches that in vivo use of altered peptide ligands is unpredictable and dangerous in outbred human populations (especially paragraph spanning columns 1 and 2 on page 370). Anderton et al further teaches that to identify TCR antagonists, the need exists to generate T cell clones for in vitro analysis, with the result that often T cells are produced and are dominant in vitro that are robust enough to withstand the selective pressures of cloning, but are not representative of the entire in vivo repertoire.

It would require undue experimentation to determine which of the trillions of peptides encompassed by the claimed invention of fragments/polypeptides comprising/compositions thereof are capable of binding to an undisclosed number of HLA molecules and which immunogenic and which are not in the context of HLA/CTL combinations. Further, synthetic peptides that are chosen on the basis of scanning the protein of interest for potential peptide sequences that have a motif for binding to an HLA molecule or molecules may not induce a CTL response due to lack of Th support for CTLp to CTL.

Accordingly, there is a high level of unpredictability in designing/selecting sequences that would still maintain function, and applicant does not provide direction or guidance to do so. Because of this lack of guidance, extended experimentation that would be required to determine which substitutions/deletions/additions or permutations of amino acids would be necessary to retain activity, and it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have activity. In other words, since it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and use the corresponding peptides. Therefore, undue experimentation would be required to determine what peptides could or could not be used in the claimed invention.

The specification does not adequately teach how to effectively use the claimed fragments/polypeptides comprising/compositions thereof capable of binding to an undisclosed number of HLA molecules and which are immunogenic in the context of HLA/CTL combinations in vivo. The specification does not teach how to extrapolate data obtained from in vitro binding and T cell stimulation assays to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the peptides exemplified in the specification and encompassed by the claims.

In view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to make and/or use the claimed invention with a reasonable expectation of success

There is insufficient guidance in the specification as to how to make and/or use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. The enablement provided by the specification is not commensurate with the scope of the claims. See In re Wands 8 USPQ2d 1400 (CAFC 1988).
Applicant's arguments in the amendment filed 12/1/04 have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on pages 7-9.

It is the Examiner's position with regard to Applicant's arguments about a peptide comprising at least 14 consecutive amino acid residues of SEQ ID NO: 5 that does not consist of SEQ ID NO: 12, that the relevant issue is that the claims encompass a peptide comprising at least 14 consecutive amino acid residues of SEQ ID NO: 5 that does not *contain* SEQ ID NO: 12, and although the skilled artisan could make a fragment of SEQ ID NO: 5 that is at least 14 amino acid residues in length, those that do not contain the minimal epitope SEQ ID NO: 12 (a 14-mer), for those fragments the specification does not teach the use wherein the fragments do not bind to HLA-B*3501 and stimulate a CTL response. It is the Examiner's further position with regard to Applicant's arguments about an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 12 wherein the polypeptide is not a subsequence of the alt.M-CSF protein, the claims are not limited to polypeptides comprising one of SEQ ID NO: 5 or SEQ ID NO: 12 and further comprising sequences that Applicant has provided in the specification for use in polytopes, i.e., other immunogenic peptides from other tumor rejection antigens. Although the hybrid or fusion polypeptides or polytopes can be made, the specification does not disclose use of compositions comprising polypeptides comprising SEQ ID NO: 12 and other tumor associated rejection antigen peptides for testing in vitro or administration in vivo for any patient or tumor type, and hence the skilled artisan would not know how to use the said polytopes to induce an immune response against renal carcinoma cells that present SEQ ID NO: 12, i.e., may not be relevant for use with SEQ ID NO: 12.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 3, 65, and 71 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 11, 2005

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